REMARKS

Claims 10, 11 and 14-24 were pending in this application. Claims 11-17 and 21-24 have been canceled without prejudice to Applicant's rights to pursue any cancelled subject matter in a continuation or divisional application(s). Claim 10 has been amended solely to promote the allowance of the case and without acquiescing to the Examiner's rejections. The amendment is supported by claims 14-19. No new matter has been added.

Upon entry of these amendments, claims 10, 18-20 and 25 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

I. Rejection over D'Amato, Kaplan , Keane and Allen Should Be Withdrawn

A. The instant claims are not obvious because the cited references do not teach or suggest the claimed methods for treating idiopathic pulmonary fibrosis

Claims 10, 11 and 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over D'Amato (U.S. Patent No. 5,593,990, hereinafter "D'Amato") and Kaplan *et al.* (WO 92/14455, hereinafter "Kaplan") in view of Keane *et al.* (*Am. J. Respir. Crit. Care Med.* 164:2239-2242, 2001, hereinafter "Keane") and Allen *et al.* (*Respir. Res.* 3(13), 2002, hereinafter "Allen"). In particular, the Examiner alleges that (1) D'Amato discloses methods of inhibiting angiogenesis and treating angiogenesis-related diseases with thalidomide; and that (2) Kaplan discloses methods for controlling TNF-α concentration with thalidomide (Office Action, pages 3-4). It is also alleged that as both angiogenesis and TNF-α are implicated in the pathogenesis of idiopathic pulmonary fibrosis (IPF) as evidenced by Keane and Allen, the skilled artisan would have been imbued with at least a reasonable expectation that a compound that inhibits both angiogenesis and TNF-α would be an effective treatment for IPF. (Office Action, pages 4-5). This rejection is respectfully traversed.

The current standard of obviousness takes into account (1) whether there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) whether there would have been a reasonable expectation of success. *See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007) ("The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed

process, and would have had a reasonable expectation of success in doing so.") (internal quotations omitted).

The cited references fail to establish the obviousness of each limitation found in the claimed subject matter: the oral administration of thalidomide in the recited dosages for the specific treatment of IPF. *In re Ochiai*, 71 F.3d 1565, 1572. (Fed. Cir. 1995) (PTO must establish "that the invention as claimed in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations."). To wit, as discussed below, the Office fails to meet the legal threshold for a finding of obviousness because the cited references would not have provided a reason to select thalidomide in specific amounts for the treatment of IPF and would not have provided the legally required expectation of success.

First, neither D'Amato nor Kaplan teach or suggest the treatment of IPF. Notably, the Examiner acknowledges that D'Amato and Kaplan differ from the claims in that neither reference discloses the treatment of IPF. Office Action, page 4. Absent any teaching or suggestion of the treatment of IPF, one skilled in the art would not have had any reason to focus on IPF, much less have an expectation of success. *See, e.g., PharmaStem*, 491 F.3d at 1364 ("an invention would not be invalid for obviousness if the inventor would have been motivated to...try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave...no direction as to which of many possible choices is likely to be successful.").

Indeed, D'Amato and Kaplan teach away from the claimed invention, because they are silent as to treating IPF, but only disclose numerous angiogenesis-related diseases (Columns 1-3 of D'Amato) or TNF-α-related diseases (pages 4-6 of Kaplan). For purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.)

Further, D'Amato does not provide a reason to specifically select thalidomide from the plethora of the compounds and general formula (Figures 1-5 and Columns 6-9). The Court held that it was <u>not</u> obvious to select one compound out of a prior art reference that disclosed a large amount of compounds, in part, because "[r]ather than identify predictable

solutions..., the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda,* 429 F.3d 1350 at 1360 (citing *In re Dillon*, 919 F.2d 688 at 692. To establish a *prima facie* case of obviousness when a prior art reference discloses a genus, the Office must show "[s]ome motivation to select the claimed species or subgenus [from] the prior art." ((MPEP §2144.08) (emphasis added). The PTO has failed to point out to any disclosure or suggestion in D'Amato that would motivate a skilled artisan to select thalidomide for IPF treatment.

Similarly, Kaplan merely discloses the use of a broad genus of piperidine derivatives for controlling abnormal concentrations of TNF-α (page 7-9). Kaplan does not teach or suggest the use of thalidomide for the treatment of IPF. Kaplan provides no reason to specifically select thalidomide from the laundry list of the compounds disclosed in the reference. Kaplan does not provide a motivation to arrive at the claimed methods.

Keane and Allen do not cure the defects of D'Amato and Kaplan because they are silent about the use of thalidomide. The Office has not pointed to any portion in Keane and Allen that would have led one skilled in the art to use thalidomide for treating IPF. In either Keane or Allen, there is no teaching or suggestion that thalidomide is effective to treat IPF. The Office appears to allege that it would have been obvious to administer thalidomide to patients having IPF, because Keane and Allen teach that angiogenesis and TNF-α are implicated in the pathogenesis of IPF, and angiostatic chemokine IP-10 and TNF-α inhibitor pirfenidone showed promising results in treating IPF. Office Action, pages 4-5. However, the fact that chemokine IP-10 and pirfenidone, *i.e.*, not thalidomide, was effective actually begs the question of why one skilled in the art would choose to pursue thalidomide over those agents. Chemokine IP-10 and pirfenidone disclosed in Keane and Allen have entirely different structures and properties from thalidomide. If chemokine IP-10 or pirfenidone was effective for IPF, one skilled in the art would have considered those agents and would not have found it obvious to pursue thalidomide. Indeed, Keane and Allen teach away from the claimed invention by not disclosing the use of thalidomide, but focusing only on the uses of the other agents. *In re Peterson*, at 1331 (Fed. Cir. 2003). Thus, one of skill in the art would have had no reason to specifically select thalidomide within the instant claims.

Furthermore, the combined teachings do not provide the legally required reasonable expectation of success. The Patent Office has not presented evidence to demonstrate that thalidomide would be effective in treating IPF. Without such evidence, no reasonable expectation of success exists because a reasonable expectation of success requires more than a motivation to simply "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result...." *Medichem v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (*quoting In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988); *see also KSR Int'l Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1739 and 1742 (2007) (an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results"). Furthermore, the courts have long recognized the unpredictability of the biological properties of chemical compounds. *See, e.g., In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties...").

Further, the etiology of IPF and the mechanism of actions are unknown, and there are many cytokines associated with IPF, including IL-6, TGF-ß1 and platelet-derived growth factor. *See* Horton *et al.*, 2008 (reference C-185) and Tabata *et al.*, 2007 (reference C-182) submitted with Information Disclosure Statement on December 23, 2008. D'Amato and Kaplan teach two different mechanism of actions and different lists of diseases, none of which include IPF. Thus, a person skilled in the art would not recognize that angiogenesis or TNF-α is the primary factor responsible for IPF and/or that the use of an angiogenesis or TNF-α inhibitor would treat IPF. Accordingly, even considering the disclosure of Keane and Allen, one of ordinary skill in the art would not expect that every compound demonstrating angiogenesis and TNF-α inhibiting activity would be useful in treating IPF. Without more specific guidance in the art, no reasonable expectation exists to the instant methods for treating IPF using thalidomide. Because the Patent Office has not presented sufficient evidence of a reasonable expectation of success, a *prima facie* case of obviousness has not been made.

The rejections is not based on the proper teachings of the cited references but only with improper hindsight. As the Supreme Court emphasized in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), "a patent composed of several elements is <u>not</u> proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." As the Court explained, "inventions in most, if not all instances rely upon

building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* Applicant respectfully requests that this rejection be withdrawn.

B. The instant claims are further unobvious because the cited references do not teach or suggest other limitations of the claims

In addition to the specific compound and disease limitations discussed above, the references also fail to render obvious other key inventive limitations found in the instant claims: orally administering thalidomide in the specific dosage range of 100 to 400 mg per day. The PTO has failed to establish that each of the claim limitations is taught or suggested in the prior art, as required for a *prima facie* case of obviousness. *See, e.g. In re Ochiai*, at 1572. (Fed. Cir. 1995).

Further, the instant claims recite, *inter alia*, the administration of a stereoisomer of thalidomide. The Examiner has not established the obviousness of administering the recited stereoisomer. Because a stereoisomer of a pharmaceutical compound can be nonobvious in view of a prior disclosure of the compound's racemate, obviousness cannot be established by the Office. *See, e.g., Sanofi-Synthelabo v. Apotex*, 470 F.3d 1368 (Fed. Cir. 2006); *Forest Labs., Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007), *aff'g* 438 F. Supp.2d 479. It is well known in the chemical arts that the separation and/or preparation of specific isomers is not predictable, nor are these processes always routine. *See, Forest*, 438 F.Supp.2d at 493. Thus, there is no motivation to select the stereoisomer, nor would there be a reasonable expectation of success in separating the isomers to yield it successful in treating IPF.

For at least the reasons set forth above, the instant claims are not obvious over the cited references, and the rejection should be withdrawn.

C. There are sufficient unexpected results to rebut even a *prima facie* case

Even assuming, *arguendo*, a *prima facie* case of obviousness was established, there is evidence of unexpected results of treating IPF with thalidomide that rebuts any such *prima facie* case. As the Examiner is well aware, even a *prima facie* case of obviousness may be overcome with evidence of unexpected results. *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646

(Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004); *see also* MPEP §2145. This requirement remains unchanged following the decision in *KSR International Co.*, as the Federal Circuit has made clear in *In re Sullivan* 498 F.3d at 1351. As the Court explained, "[w]hen a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." *Id.* at 1351. Such rebuttal evidence includes "evidence of unexpected results." *Id.*, citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007).

Applicant respectfully invites the Examiner's attention to Horton *et al.*, 2008 submitted as reference C-185 on December 23, 2008. Horton *et al.* reports on a study where 11 patients with IPF were orally administered with thalidomide in 100-400 mg per day. *Id.* The authors observed that 10 patients showed resolution of IPF with thalidomide. *Id.* Applicant respectfully submits that these results are sufficient to rebut any presumption of obviousness that may have been established by the references cited in the Office Action. In view of these unexpected results, the instant claims are not obvious. *In re May*, 574 F.2d at 1094. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

II. Rejection further in view of Selman Should Be Withdrawn

Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over D'Amato and Kaplan in view of Keane and Allen as applied to claims 10, 11 and 14-20 above, and further in view of Selman *et al.* (*Chest* 114:507-512, 1998, hereinafter "Chest") (Office Action, pages 5-6). Applicant respectfully disagrees.

Claims 21-24 have been canceled solely to promote the allowance of the case and without acquiescing to the Examiner's rejection. Accordingly, the rejection is moot and should be withdrawn.

III. Rejection over Banerjee Should Be Withdrawn

Claims 10, 11 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banerjee *et al.* (US 2004/0131614, hereinafter "Banerjee") in view of Kaplan. (Office Action, pages 6-7). This rejection is respectfully traversed.

Claims 11 and 21-24 have been canceled. Therefore, the rejection is moot with respect to these claims.

It is alleged that because Banerjee teaches a method for treating IPF by administering TNF-α antibodies alone or in combination with other therapeutic agent such as thalidomide, it would have been a *prima facie* obvious to a skilled artisan to have administered a combination of TNF-α antibodies and thalidomide for the treatment of IPF. (Office Action, pages 6-7). Applicant respectfully disagrees.

Amended claims 10 and 18-20 do not recite the use of a combination of a TNF-α antibody and thalidomide. Amended claims recite the oral administration of thalidomide alone in the specific doses which were recited in canceled claims 14-18. Claims 14-18 are not rejected under this section over Banerjee in view of Kaplan. Thus, this rejection is moot.

Further, Banerjee teaches away from the claimed invention as it focuses on the use of TNF-α antibodies rather than thalidomide. Accordingly, the pending claims are not obvious over Banerjee in view of Kaplan.

IV. Rejection of Claims 14-18 Should Be Withdrawn

Claims 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banerjee in view of Kaplan as applied to claims 10, 11 and 19-24, and further in view of D'Amato. (Office Action, pages 7-8). This rejection is respectfully traversed.

Claims 14-17 have been canceled. Therefore, the rejection is moot with respect to these claims.

Amended claim 18 depends on claim 10. Since claim 10 is not rejected over Banerjee, the rejection of claim 18 which depends on claim 10 should be withdrawn. Claim 18 recites all limitations of claim 10 plus wherein thalidomide is administered in an amount of 100 mg, 200 mg, 300 mg or 400 mg per day. Because claim 10 is not obvious over the cited references for the reasons discussed above, claim 18 is also not obvious. The PTO has failed to establish that each of claim limitations is taught or suggested in the prior art, as required for a *prima facie* case of obviousness. *See, e.g. In re Ochiai*, at 1572. Thus, Applicant respectfully requests withdrawal of the rejection of claim 18.

Conclusion

Applicant respectfully requests that the above amendments and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

No fee, other than an extension of time fee for one month, is believed due. Please charge any required fees or credit any overpayment to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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